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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,029	07/30/2001	Frits Jacobus Fallaux	3833.5US	1408

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/918,029	Fallaux
Examiner	**Art Unit**
Dave Nguyen	1632

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 2, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-8 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on 7/30/01 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ *Some** c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 08/793,170 .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claim 1 has been amended; Claims 6, 7 have been added by the amendment filed December 2, 2002.

Applicant's election without traverse of the species of SEQ ID NOS: 19 and 20 in the response filed December 2, 2003 is acknowledged. However, none of the pending claims recites the sequences, and thus, the species restriction has been withdrawn by the examiner.

Claims 1-8 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a genus of unspecified recombinant nucleic acid molecules derived from a linear precursor recombinant nucleic acid molecule based on an adenovirus, wherein said precursor recombinant nucleic acid molecule comprises at least one functional inverted terminal repeat, and wherein the precursor recombinant nucleic acid molecule comprises at the 3'terminus a sequence complementary to an upstream part of the same strand of the precursor recombinant nucleic acid molecule. The as-filed specification mainly describes that by synthetically or recombinantly placing a DNA sequence at the 3' terminus of an adenovirus based precursor nucleic acid sequence comprising at least one ITR, the recombinant adenovirus based precursor nucleic acid sequence would form a hair pin structure, wherein the free 3'-hydroxyl group of the 3' terminal nucleotide of the hair pin structure can serve as a primer for DNA

synthesis. In order to practice the full scope of the claimed invention, one skilled in the art would turns for guidance from the as-filed specification for a description of the material(s) essential for the practice the full scope of the claimed invention, *e.g.,* a genus of derivatives of the described recombinant adenovirus based precursor nucleic acid sequence. However, other than detailed description of preparation and making of a recombinant adenovirus based precursor nucleic acid sequence as indicated above, the as-filed specification including its incorporated references do not provide a description of the essential material(s) as required by the full scope of the presently pending claims. Thus, it is not apparent how one skilled in the art, on the basis of the written description of this instant application, could envision a representative number of the derivatives other that the described recombinant adenovirus based precursor nucleic acid sequence. Claiming all nucleic acid vectors that achieve a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A recombinant adenovirus based nucleic acid molecule comprising at least one functional inverted terminal repeat, and wherein the precursor recombinant nucleic acid molecule comprises recombinantly fused at the 3'terminus a sequence complementary to an upstream part of the same strand of the precursor recombinant nucleic acid molecule.

The specification does not reasonably provide enablement for the presently pending claims encompassing any other derivatives as embraced and yet being unspecified by the as-filed specification.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the full scope of the claims for the reasons set forth above, one skilled in the art would not known how to use and make the full scope of the claimed invention so that it would operate as intended without undue experimentation.

Regarding the terms "wherein said E2A region is mutated so that at least one of its products is temperature sensitive", and "host range mutation" as recited in the claims, since the nucleic acid sequence encoding a particular protein determines the protein's structural, and functional properties, predictability of which changes can be tolerated in the nucleic acid sequence and still retain similar functionality of the protein requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional determinants and functional usefulness. Furthermore, the problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable; and, thus, it is not apparent how one skilled in the art arrives at all claimed nucleic acid sequences that exhibit a biological activity, *e.g.* packaging activity (see claim 1), without undue experimentation (see Ngo *et al.*, in: The Protein Folding Problem and Tertiary

Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). The specification does not provide guidance and/or evidence for one skilled in the art to determine, without undue experimentation, as to which mutations other than a temperature sensitive 125 mutation and a host range mutation in the hr400-404) mutation(s), would exhibit the functional properties as recited in claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1and claims dependent therefrom, the recitation of "a recombinant nucleic acid molecule derived from" does not particularly point out what are exactly the structural materials as intended by application for the claimed invention, and neither the specification nor the claims provide any description of the derivatives. As such, one skilled in the art would not be able to envision as to what are exactly intended by applications for the metes and bounds of the claims, particularly on the basis of the applicant's disclosure.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United

States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5-8 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a), as being unpatentable over either Imler (US Pat No. 6,040,174) or Kovesdi *et al.* (US Pat No. 5,994,106).

Both Kovesdi *et al.* and Imler *et al.* teach identical packaging cell that produces stocks of recombinant replication-deficient adenovirus based DNA. It is apparent to one of ordinary skill in the art that from the disclosures of Kovesdi *et al.* and Imler *et al.*, as long as an inducible promoter is employed to drive, control, and regulate expression of at least the E1A adenovirus gene product, a recombinant replication-deficient adenovirus based DNA comprising two ITR can be produced. Thus, absent evidence to the contrary, the recombinant replication-deficient

adenovirus based DNA of the prior art are the same as the derived recombinant nucleic acid molecules.

Claims 1-8 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a), as being unpatentable over Wilson *et al.* (US Pat No. 5,652,224).

To the extent the claims are readable on derivatives of adenovirus based nucleic acid sequences comprising a gutless adenovirus vector comprising two ITR, Wilson *et al.* disclose a replication defective adenoviral vector which is deficient in a function provided by region E1 in combination with a deficiency in region E2, *i.e.*, E2A, E2B, or both E2A and E2B (column 9). Wilson *et al.* further teach that in order to provide the necessary materials for packaging the adenoviral vectors into viral particles, a packaging defective helper virus containing a transcription initiation regions operably linked to adenoviral genes encoding the packaging materials is employed for producing replication defective adenoviral particles, *e.g.*, E2A, E1A and E1B(column 13). More specifically, Wilson *et al.* disclose a minimal adenovirus containing only the adenovirus cis-elements necessary for replication and virion encapsidation, to otherwise deleted of all adenovirus genes. The minimal adenovirus of Wilson *et al.* contains the cis-acting 5' and 3' inverted terminal repeat (ITR) sequences of an adenovirus and the native 5' packaging/enhancer domain, that contains sequences necessary for packaging linear adenoviral genomes, and a heterologous expression cassette located between the ITR sequences (column 9). Wilson *et al.* further teach that those gene sequences not present in the adenovirus portion of the vector must be supplied by either a packaging cell line and/or a helper adenovirus to generate the replication defective adenoviral particles (columns 9-10, 12). Wilson *et al.* also teach that the mini adenovirus vector can contain additional adenovirus gene sequences, which then are not required to be supplied by a helper gene (column 10, lines 18-20). Methods using inducible promoters for controlling gene expression *in vitro* are disclosed at column 8. Methods using a temperature sensitive E2A gene in the packaging construct is disclosed at column 11. Since nucleotide residues encoding the hr400-404 mutation are known in the art at the time the invention was made, as evidenced by page 11 of the as-filed specification, it would also have

been obvious for one skilled in the art as a mater of optimum choice for replication in a suitable packaging cell to make and use the temperature ts121 mutation and/or the hr400-404 mutation.

Absent evidence to the contrary, or in the alternative, the recombinant expression vectors and packaging constructs of Wilson *et al* are the claimed derived recombinant nucleic acid molecules

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER